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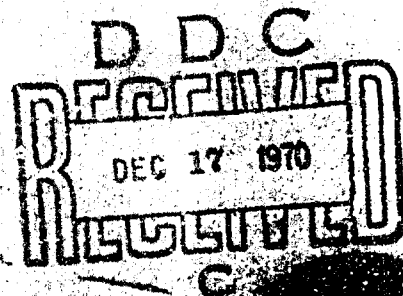


Some Acute and Chronic
Effects of
Endrin on the Brain

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SOME ACUTE AND CHRONIC EFFECTS OF ENDRIN ON THE BRAIN

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ACKNOWLEDGMENTS

Mrs. Virginia Leonard and Mrs. Martha Mathis were largely responsible for the excellent animal care and resourceful execution of the experimental protocol which made this study successful. I am profoundly grateful to them. My thanks are also due Dr. Paul Smith of this laboratory for his helpful guidance and comments.

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SOME ACUTE AND CHRONIC EFFECTS OF ENDRIN ON THE BRAIN

I. Introduction.

Until the chlorinated hydrocarbon pesticides (CHPs) are more sharply limited in use they will continue to present a potential hazard to aerial applicator personnel: The CHPs are neurotoxins which can, in sufficiently high doses, cause behavioral disorders, convulsions and death (Winteringham and Barnes, 1955/ James and Davis, 1965; Hayes, 1965). Although applicators seldom receive single doses of these compounds large enough to cause seizures, it is necessary to evaluate whether brain functions can be affected by: 1. subconvulsive single doses, or 2. chronic exposure.

Toxic concentrations of CHPs in the brain can arise in two ways. Accidental exposure may occur and absorption of the CHPs can then result in acute poisoning. More generally, CHPs are present in and absorbed from our environment. These CHPs are stored in varying amounts in body fat and lipid (Hayes, 1965), and this chronically stored CHP could also represent a hazard if: a) continuous release from storage occurred at a "significant" rate; b) sufficient amounts could be released from storage by stimuli such as starvation or emotional stress; c) some quantity of CHP was strongly bound to nerve cell membrane and thus caused a "permanent" alteration in the functions of the neurone. Some direct or speculative evidence can be adduced for each of these possibilities (e.g. Date et al., 1962; Haymaker et al., 1946) but more information seemed desirable in view of the potential hazards involved.

Such information, on the mechanisms of the toxic actions of the CHPs on the brain, is useful in two ways. Knowledge about the effects on the brain can be used to predict the exposure levels at which performance changes may be expected in exposed aerial applicator personnel. The changes in brain functions, mirrored in EEG shifts, may be useful in the diagnosis of or evaluation of the extent of poisoning.

Two series of experiments were initiated: one was designed to analyze of acute administration of selected CHPs on the brain, the second to analyze the consequences of chronic exposure to CHPs. In both studies, changes in brain bio-electrogenesis were used as indices of CHIP action. Two types of brain potentials were studied. Evoked potentials (EPs) are those induced in specific brain-nuclei by stimuli controlled by the experimenter. The EPs are easy to analyze and were intended to be the primary data of these experiments. Spontaneous activity as recorded on the electro-encephalogram (EEG) is that occurring in the absence of any overt external stimuli. The EEG is a sensitive qualitative indicator of drug actions but is very difficult to quantitate or analyze (Fink, 1969).

It would be most desirable to test the effects of the CHPs directly in man. However, in toxicity studies, such as this, it is necessary that dosage be manipulated over a very large range. This cannot be done with the CHPs in man due to the extremely hazardous nature of these compounds. Consequently, these experiments were designed for and executed in animals selected, as will be noted, for their applicability to the questions to be asked.

Anecdotal evidence from aerial applicator personnel available in this laboratory suggested that CHP's, particularly endrin, significantly affected visual mechanisms in the brain. Studies in animals lend some support to this (Bundren et al., 1952; James and Davis, 1965). This hypothesis, though speculative, did suggest the choice of the neuronal pathways used in our studies. Revzin and Karten (1966/67) have described an avian visual projection pathway from retina to optic tectum, thence to nucleus rotundus thalami and thence to ectostriatum (a large telencephalic nucleus). The rotundo-ectostriatal projection offers unique advantages as a neuropharmacological test site, for nucleus rotundus has only one set of afferent fibers, that from the optic tectum (Karten

and Revzin, 1966) while ectostriatum has but two sets of afferents, that from rotundus and from the ascending reticular activating system (ARAS). Thus, recording electrodes in ectostriatum can sample responses to two, and only two, input systems. Such isolation greatly simplifies the interpretation of drug effects. Consequently, the acute experiments were done on anesthetized pigeons. It was also desirable to extend the results to mammals, and to do chronic studies which are technically difficult in pigeons. Therefore, squirrel monkeys (*Saimiri sciureus*) were used in the chronic studies.

Endrin is the most toxic of the commonly available CHPs (Radeleff, 1964), and was a source of great concern when these studies were begun. Therefore, both acute and chronic experiments were done using endrin. DDT and lindane have also been studied in the acute experiments since they represent other groups of CHPs in use.

II. Methods.

A. *Pigeon*. Urethane anesthetized white carneau pigeons were used. The animals were held in a special head holder. Electrodes were positioned stereotaxically (Karten and Hodos, 1965) and their location was confirmed histologically at the end of the experiment, using frozen sections of the brain stained with cresyl violet acetate. The recording electrodes were micropipettes filled with 3M NaCl with a tip resistance of around one megohm. Stimulating electrodes were 3-barrelled micropipettes (Tripettes) with an over-all tip diameter of about 50 μ m, filled with either 3M NaCl or with 0.9% NaCl solutions. The small size of these tripettes permitted stimulation of very small tissue volumes, a desideratum in the small brain of the pigeon. Recording electrodes were positioned, usually, in hyperstriatum accessorium, neostriatum caudale and ectostriatum (Fig. 1). Stimulating electrodes were placed in nucleus rotundus thalami and in nuclei of the ascending reticular activating system (ARAS), chiefly nucleus pontis oralis. The CHPs in the pigeon were most usually given intravenously in an emulsion of corn oil and saline, the emulsifying detergent being polyoxoethylene sorbitan mono-oleate. Solutions of the CHPs in ethyl alcohol or dimethyl sulfoxide were also used. There was no qualitative difference relative to CHP effects among the solvents, nor did the sol-

vents exert any effects of their own. Conventional electrophysiological ink writing and oscillographic recording techniques were used and an ND-800 "Enhancetron" was used to compute average evoked potentials.

B. *Squirrel Monkeys*. Male squirrel monkeys (*Saimiri sciureus* weighing at least 600 grams) were anesthetized with pentobarbital and placed in a stereotaxic instrument. Bipolar stainless steel wire electrodes were positioned in visual cortex bilaterally, lateral geniculate body, superior colliculus, lateral amygdalar nucleus and ventral hippocampus. Electrodes were also positioned in the pulvinar nucleus and temporal cortex in two animals, but these leads, unfortunately, developed defects and were unusable. Wire leads were run from the electrodes to a "micro-ribbon" connector and the assembly was anchored to the animal's skull by wood screws and dental acrylic.

A standard recording sequence was followed for all animals. Two to three weeks after the surgical procedures the recordings began. Each morning the animal was placed in a conventional two-plate restraint chair and a cable was plugged in to connect the electrodes to the stimulating and recording apparatus. Stimulating pulses were derived from Tektronix waveform generators via a Bioelectric Instruments isolator. Inputs from recording electrodes were taken to a Grass Model 6 EEG machine for ink recordings of EEGs. EPs were recorded using a Nuclear Data ND-800 averager and an X-Y recorder. EEG recordings were taken from all leads. The evoked potentials recorded included lateral geniculate-visual cortex, superior colliculus-lateral geniculate and amygdala-hippocampus. Stimulus parameters and amplifier gains were constant throughout the months of the study.

A complete cycle of EEG and EP recordings was taken hourly for 8 hours, then the animal was returned to its cage. This was done for 5 days per week; the animal was then undisturbed for 2 days. After 4 weeks or more of recordings for normative data, drug administration was begun. The endrin was injected intramuscularly in a corn oil and saline emulsion. Injection volume did not exceed 0.05 cc and injections of "blank" emulsion were given throughout the "normative" and recovery periods to control for injection and solvent artefacts. The drug was injected after the second recording of the day,

so that on each day there were 2 pre-drug and 6 post-drug recordings. Drug administration was continued until seizure phenomena were seen in the EEG. Endrin injection was then stopped and recovery was followed for at least one month. Three monkeys have been studied to date, "Charlie," "Bob" and "Jim."

III. Results.

Acute Studies in Pigeons. Figure 1 summarizes the results of the evoked potential studies in anesthetized pigeons. As can be seen in the inset sketch in Figure 1, the rotundo-ectostriatal evoked potential has several components. The initial radiation response is due to the activity in the terminal ends of the nerve fibers carrying the nerve impulses resulting from the electrical stimulation of nucleus rotundus. The radiation response was not affected by any of the CHPs tested, and will not be further discussed. The late, positive-going components of the evoked potential were affected by the CHPs but the changes paralleled those seen more clearly in the negative waves (In the Figure, negative deflections are upward).

Following the radiation response there are two overlapping negative waves, the primary and secondary negative waves or responses. The significance of the negative waves may be briefly summarized. The incoming impulses from the stimulated nucleus rotundus excite the neurones in ectostriatum. The primary negative wave is a reflection of the bioelectric events occurring during this excitation. The stimulated ectostriatal neurones, in turn, excite and inhibit other ectostriatal neurones, which like those primarily stimulated, may either terminate within ectostriatum or send projections to other brain nuclei. The secondary negative wave represents, in large part, the activation of these other ectostriatal neurones. The secondary waves were seen in 40% of the animals studied.

Endrin enhanced, or facilitated, the primary negative wave of the rotundo-ectostriatal evoked response. The threshold dose for this facilitation was 0.5 mg/kg. Maximum effects of endrin were seen at around 3.0 mg/kg, a dose which was near, or at, seizure threshold. Maximum increases seen ranged up to 250% of control amplitude, although the response, even to large doses, was usually rather less than this (Figure 1). The

endrin effects began to develop within 15 minutes of injection; the maximum effects were seen in 30-40 minutes and the effects persisted for the remainder of the experiment, 6-7 hours. No statistically significant changes were seen in the secondary wave.

DDT, in contrast to endrin, had no significant effect on the primary negative wave of the response. DDT did, however, facilitate the secondary wave of the response. This was seen either as an absolute increase in secondary wave amplitude or, in larger doses, as the appearance of the secondary wave after DDT injection, when no secondary wave had been present in the control recordings. The threshold dose for this DDT effect was 25 mg/kg; maximum effects were seen at 100 mg/kg. The DDT effects appeared within 45 minutes of injection; maximum effects developed within 2 hours and persisted for the duration of the experiment, 6-7 hours (Figure 1).

Lindane affected both the primary and secondary negative waves, although, in contrast to DDT, secondary wave changes were not invariably seen. Threshold doses of lindane were 3-5 mg/kg; maximum effects were seen after 15-20 mg/kg. Lindane effects were seen within 30 seconds of the beginning of injection; maximum effects were seen within one minute and the responses to control amplitudes in 1-2 hours (Figure 1).

In summary, endrin affected the primary negative wave of the rotundo-ectostriatal evoked response, DDT affected the secondary wave, and lindane affected both. Pharmacologically, this means that endrin and DDT act, in this system at least, on different receptor sites while lindane may act on both "endrin" and "DDT" receptors. Similar conclusions regarding these CHPs have been reached, based on radically different approaches (Georghiou, 1965; Soloway, 1965). Thus, where more than one of these CHPs is present in an animal, their brain effects will be independent of each other. Note, however, that since endrin, DDT and lindane are convulsants, their effects will tend to add, phenomenologically at least. The available evidence (Revzin, 1966; Revzin, 1966 and in preparation) indicates that the CHP effects above are due to a direct action on ectostriatal neurones. Since ectostriatum is a visual system nucleus in birds, (Revzin and Karten, 1966/1967; Revzin, in preparation), these CHPs can effect visual performance in exposed

animals. It should also be noted that, for each CTP tested, the threshold dose for EP effects was around 20-25% of the seizure threshold dose. The probable significance of this will be analyzed at greater length in the general discussion.

Chronic Studies in Monkeys.

Evoked Potentials. The studies undertaken in the chronic monkeys were very largely oriented toward analyses of evoked potentials as a result of the findings in the pigeon studies. The EEG studies, reported below, were, in some respects, an afterthought. However, no significant endrin-induced changes in evoked potential characteristics were seen in this study. Some suggestive trends were present and are serving as a basis for a fresh experimental approach, but further discussion of the evoked potential data is not relevant to the present paper since the results were negative.

EEG. Spontaneous brain electrical activity was monitored at all functioning electrodes. Behavioural notes were also made in the protocol to indicate the state of the animal (sleepy, alert, excited, moving violently, etc.) during the recordings. However, the analysis of EEG records presents some difficulties. It is a simple matter to decide whether or not a seizure was present, as a brief look at Figure 2 and Figure 3 will show. It is a much more difficult matter to decide whether, and to what extent, any given recording differs from another. In practice, the combined judgments of three experienced observers were supplemented by "naive" observers from other laboratories, all looking at control and experimental recordings which were matched for "alertness," time of day and other variables. Thus, except for "seizure versus non-seizure," all the following EEG data are qualitative and must be regarded with some caution, especially with regard to threshold effects.

The first animal studied was Charlie (Figure 2). Charlie was given endrin at the rate of 0.2 mg/kg/day. After 5 days some EEG changes were seen, though admittedly very slight. As the experiment progressed, the EEG changes became progressively more severe, though the rate of change was slow. After 4 weeks, the dose rate was increased to 0.4 mg/kg/day and the rate of change of the EEG increased. After a total dose of 9.0 mg/kg the EEG changes were quite

marked with a great increase in "spiking" and high frequency activity (Figure 2). Behavioural observations, though imprecise, suggested that the behavioural changes paralleled the EEG changes. An increase in excitability or irritability was seen as endrin dosage continued, together with a variety of visual and sexual automatisms.

At a total dose of 10 mg/kg, seizures developed in all leads, though activity in amygdala is most prominent in Figure 2. During the seizure the monkeys eyelids were closed and twitching, there was some limb rigidity, and occasional clonic movements and severe salivation together with penile erection were seen. The seizure lasted about 2 minutes, and recurred at 30-40 minute intervals for about 3 hours. Full "grand mal" epileptiform seizure phenomena were not seen in any of the 3 "chronic" animals, although such patterns could be induced by much larger, and lethal, quantities (unpublished observations).

Endrin administration was discontinued after the seizures, through recordings and "blank" injections continued. Three weeks after the seizures, EEG's and behavior were still "abnormal" (Figure 2). At the end of this three weeks, recordings on Charlie were discontinued and the other two animals, Bob and Jim, were studied, seriatim. Results of these experiments were similar to those in Charlie in that EEG changes and behavior changes were seen after relatively small total doses (of the order of 0.5-1.0 mg/kg) and general electrographic seizures eventually developed. However, the daily endrin doses used in Bob and Jim were larger than in Charlie and the total doses at which seizures developed were of the order of half that for Charlie. The EEG's of Bob and Jim returned very nearly to pre-injection baseline within 2 weeks of stopping endrin.

As indicated, after their experimental trials, Charlie, Bob and Jim were simply maintained in their home cages. Over a period of months, the animals' behavior returned toward control levels, the only overt signs of poisoning being "hyperirritability" and weight loss. Then, recordings were resumed for a week or two in each animal to check long-term EEG changes, if any. The events seen during this week were identical in all animals, and will be described as they occurred in Bob, the animal receiving the lowest total dose of endrin (4.5 mg/kg).

Bob was placed in the restraint chair and recordings were begun at 10:00 A.M. on a Monday. The animal was obviously distressed by this procedure for there was much struggling and vocalization in the chair, a sharp contrast to Bob's quiet and cooperative behavior during the entire course of the main experiment. The EEG at this time showed more "spiking" than several months before, but was not strikingly abnormal and soon "quieted down" (Figure 3) as Bob's behavioral distress abated. This pattern continued without much change until 12:10 P.M. when some blinking, staring and other visual automatisms appeared. They were similar to those seen during the endrin-induced seizures in this animal and were associated with abnormal trains of spikes in the lateral geniculate body (Figure 3). The EEG abnormalities and behavioral changes became more marked until, at 12:45 P.M., full electrographic seizures developed, initially in the lateral geniculate and in striate cortex (Figure 3). The seizure pattern was identical to that induced by endrin administration 4 months before. Seizures recurred at 1:30 P.M. (Figure 3) and at 3:00 P.M. It must be emphasized that Bob had received no injections of any kind for nearly four months, and that endrin had been discontinued 17 weeks previously. The next day, Tuesday, Bob was less disturbed at being put in the chair and no seizures occurred, though the EEG seemed grossly abnormal. By Wednesday, Bob was again adapted to the experimental routine and the EEG throughout this day, and those following, resembled the 12:05 record in Figure 3—which was not very different from the control period records.

In summary, the chronic monkey studies have demonstrated that chronic administration of endrin can lead to convulsions. This was, perhaps, not surprising (Winteringham and Barnes, 1955). However, the recurrence of seizures, under stress conditions, months after termination of endrin administration demonstrates most emphatically that the endrin stored in the body after exposure can not be regarded as toxicologically inert.

General Discussion. Three general conclusions emerge from the preceding work. The first conclusion is that CHPs can affect central nervous system sensory processing at doses substantially below lethal or convulsive levels. Consequently, the performance and behavior of the

poisoned animals can be affected in the absence of the tremors and seizures generally considered to be the overt signs of CHP intoxication. Two questions arise immediately: 1. Are the conclusions valid for animals other than pigeons? 2. Do such CHP-induced changes in brain electrogenesis constitute a hazard for man. However, to take just two points, the participants in a recent symposium on "Subcortical Visual Systems in Vertebrates" (Brain, behavior and Evolution, 1970, in preparation) agreed that there is a high degree of similarity in the organization and function of the brains of reptiles, birds and mammals. Furthermore, the behavioral sequelae and seizure patterns seen after lethal doses of the CHPs were similar when tested in pigeons, rats and monkeys (Revzin, unpublished observations; Radeleff, 1964; Winteringham and Barnes, 1955). For these reasons, among many, the CHPs may be expected to cause similar, but not necessarily identical, brain dysfunctions in all vertebrates.

It is more difficult to address the question of the extent of the hazard posed by the effects on the brain of sub-lethal doses of CHPs. The answer to this question becomes primarily a question of dose, how much CHP is present, the time interval over which exposure occurs, the amount of stored CHP and so forth. Thus, the answer to *this* question is intimately involved with the second general conclusion from the reported work, and will be discussed with it in the following paragraphs.

The second general conclusion of this paper is that CHPs "stored" in body fat or lipid are not toxicologically inert but, rather, can be mobilized and may then cause toxic responses in the brain. This was shown by the recurrence of seizures in monkeys some four months after endrin injections had stopped. The mechanism for the seizure recurrence is obscure. The CHPs could have been released from body fat as a sequelae of emotional stress, or the compounds could have been bound in the brain substance and thus have altered the response of the central nervous system to stress conditions. The author prefers the former explanation, although available data is inconclusive. It is extremely unlikely that the seizures were a mechanical artefact caused, say, by movements of the plug-electrode assembly. Consider the following points: the seizures developed over two to three hours *after* the animal was connected to the apparatus; the seizures were seen only on the

first day of recording and the EEG abnormalities quickly vanished as the animals readjusted to the experimental situation; the seizure developed in all three animals; there was no anatomical evidence of unusual or extensive damage at the sites of electrode tips. Taken together these points indicate, as stated, that the seizures were not an artefact of local mechanical damage to the brain.

The animals showing stress-induced seizures had received total endrin doses of 4.5 mg/kg or more; 4.5 mg/kg is a very large dose of endrin which, at a very rough estimate, would lead to concentrations in the fat of monkeys of about 25 ppm, after four months. The pigeon studies quoted, and some (unpublished) toxicity studies showed that the ratio of the threshold dose for EP changes to the threshold dose for seizures was about 5:1 for endrin, 10:1 can be assumed to be conservative and allow for methodological uncertainties. Thus, if stress to an animal carrying 25 ppm of endrin in its fat can induce seizures, the same stress to an animal storing 2.5 ppm may induce EEG or EP and, presumably, behavioral changes. Again, to be conservative, it appears that 0.5 to 1.0 ppm of endrin in body fat brain of man or animals *might* be hazardous. Note that these "potentially hazardous levels" are crude estimates based on a variety of data on rates of elimination, metabolic patterns and percentage of body fat in the animals concerned. Possibly for this reason, possibly because stress release causes higher than normal *blood* levels of CHPs (Keane and Zvon, 1969), the "potentially hazardous levels" estimated above are lower than those usually cited as causing toxic reactions (Winteringham and Barnes, 1955). However,

the above estimated "hazardous" levels are also considerably above the levels generally encountered in the human population (Hayes, 1965). In this respect, at least, the CHPs cannot presently be called health hazards to the general public, but occupationally exposed persons such as aerial or other applicator personnel may well have hazardous CHP levels. This is cause for legitimate concern since it could be associated with impaired performance and subsequent aircraft accidents.

The third general conclusion from these data is that EEG phenomena will probably be useful in diagnosis of poisoning due to CHPs. The EEG changes were seen in all animals, were consistent in pattern and appeared at relatively low doses of the CHPs. It thus seems likely that the CHP-induced *changes* in the EEG (increases in amplitude, frequency, and "spiking"; decreases in alpha-type activity) can be used as a basis for diagnosis of poisoning although much more work is needed to isolate the relevant diagnostic criteria.

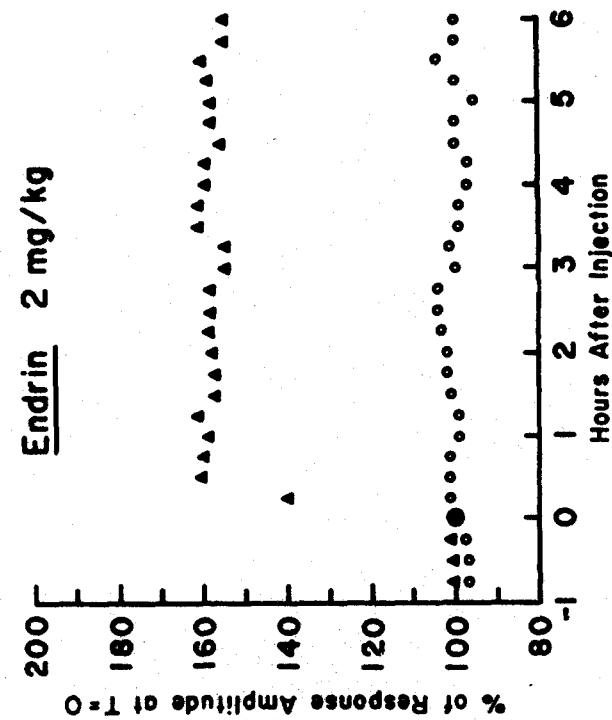
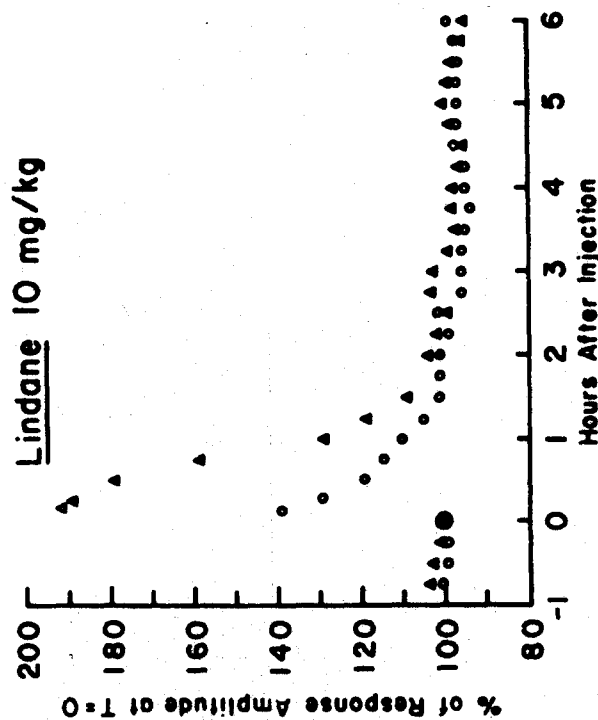
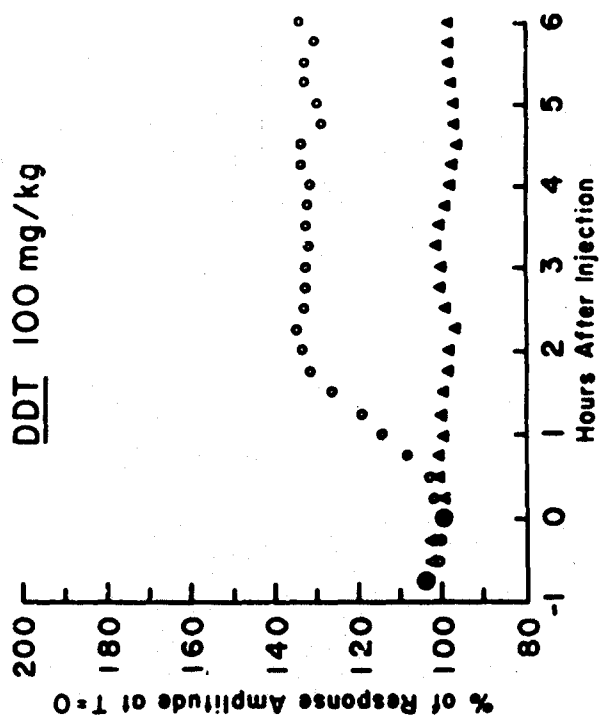
IV. Summary.

Evidence is presented showing that pesticides can affect brain bioelectric phenomena at doses well below those causing seizures or other gross behavioral changes. Chronic administration of high levels of endrin induced seizures in squirrel monkeys. Some months after termination of endrin administration, the seizures recurred, under stress conditions. It is suggested that this phenomenon may be due to a stress-induced release of endrin from body fat. Some implications of these findings for aerial applicator personnel are discussed.

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Diagrammatic Evoked Potential

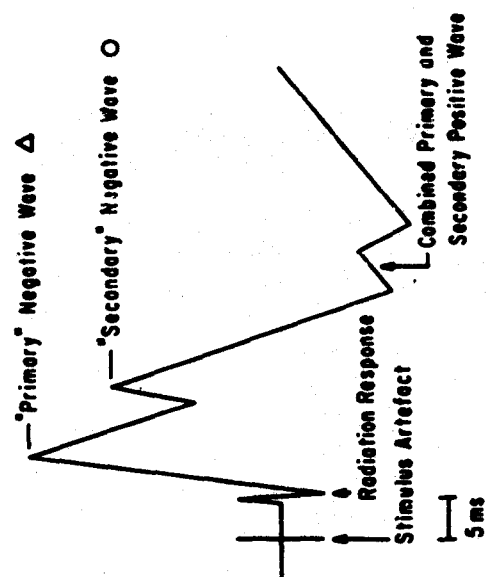
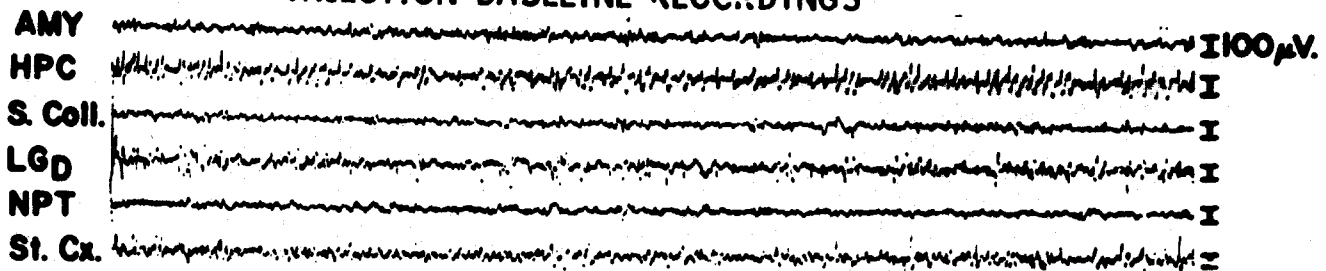


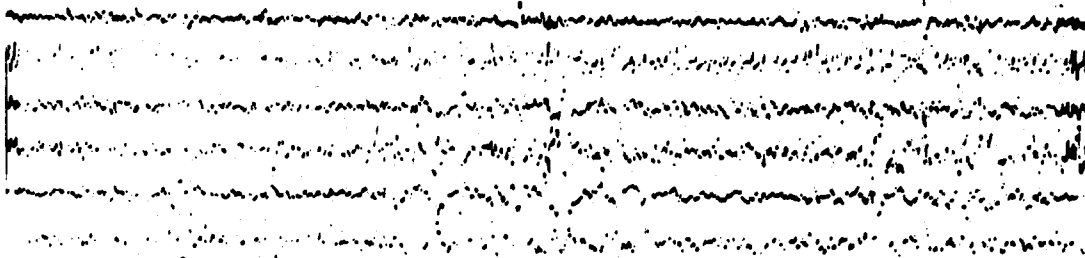
FIGURE 1. Changes in peak amplitudes of the primary and secondary waves of the rotundo-ectostriatal evoked response are shown as a function of time after injection of lindane, DDT and endrin at the noted doses.

CHARLIE

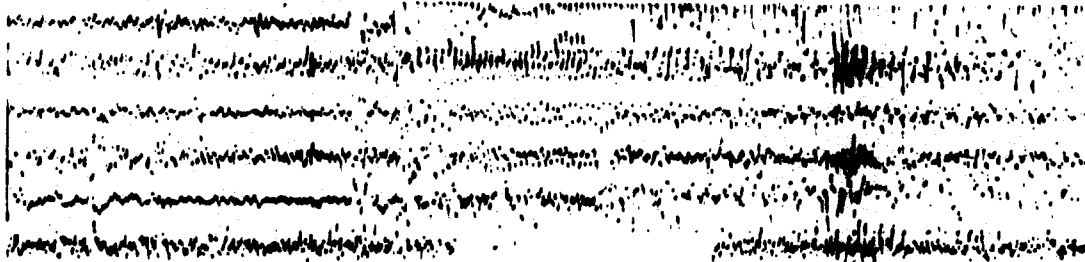
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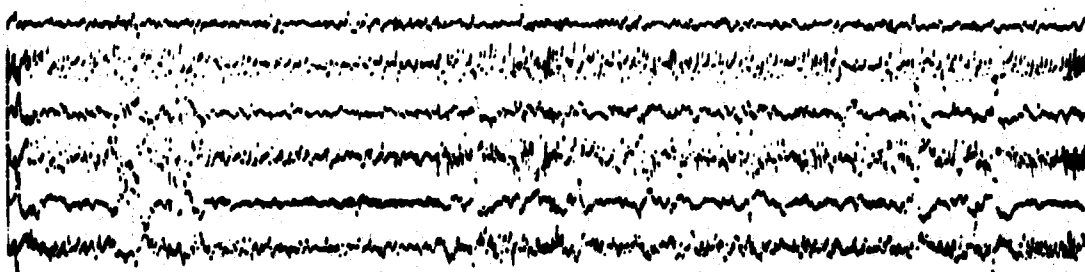
Total dose 9mg/kg IM



Total dose over 2 mos. \approx 10 mg/kg IM



RECOVERY

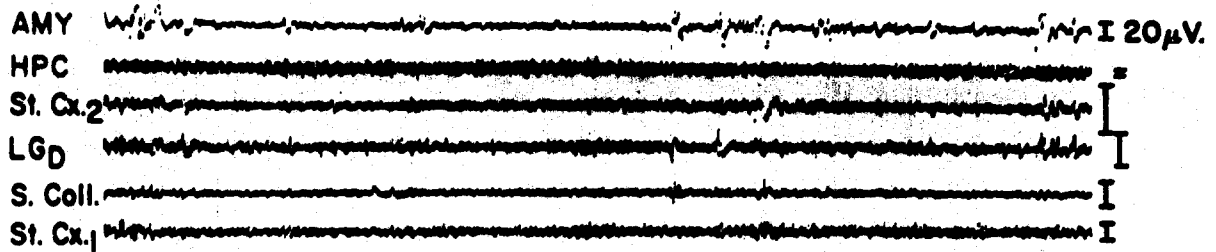


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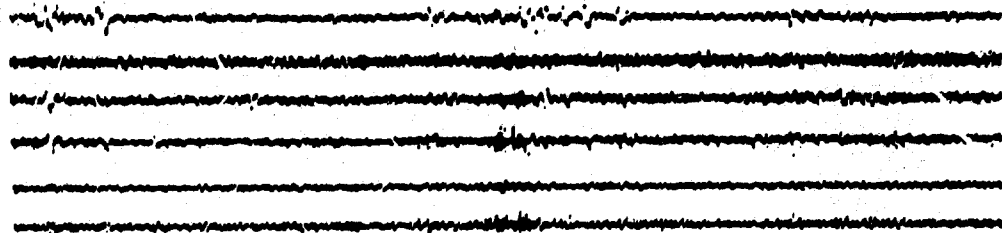
FIGURE 2. EEG records taken from the monkey "Charlie" before, during and after chronic endrin injection—the control record was taken just before drug injection began. The "9 mg/kg" record was taken 8 weeks after the control. The "10 mg/kg" record was taken 1 week later and the recovery record was made 3 weeks later still. Abbreviations: AMY, lateral amygdalar nucleus; HPC, ventral hippocampus; LGD, lateral geniculate body; NPT, posterior thalamic nuclear complex; S. Coll, superior colliculus; ST. Cx., striate cortex.

BOB

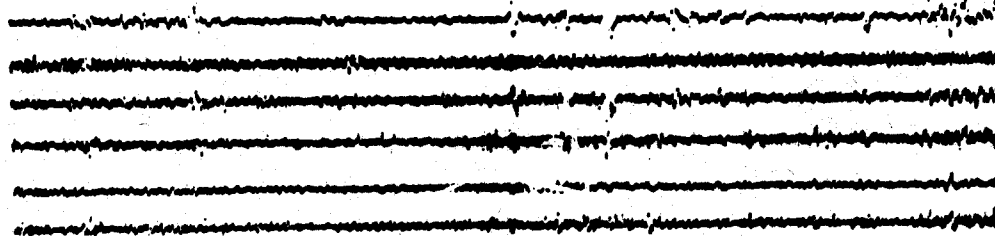
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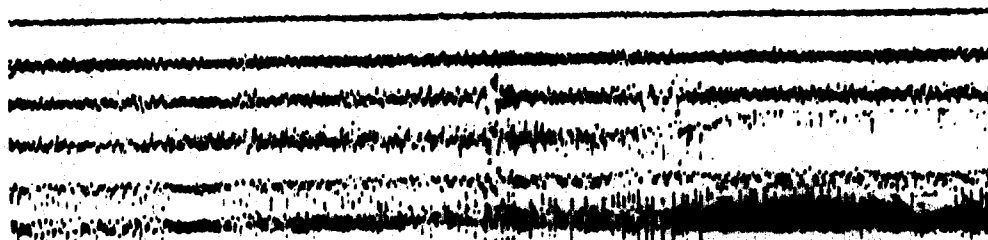
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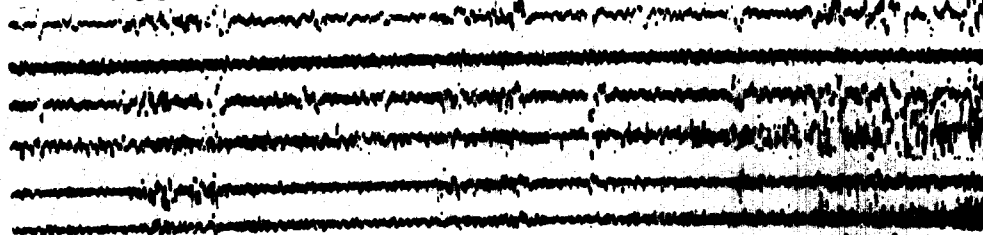
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FIGURE 3. Records from "Bob" taken 17 weeks after Andrin was discontinued and 14 weeks after the last previous recording. Note development of seizures 2 hours and 45 minutes after the first recording or about 8 hours after the animal was placed in the restraint chair. Similar phenomena were seen in the other animals. Abbreviations: AMY, lateral amygdalar nucleus; HPC, ventral hippocampus; LG, lateral geniculate body; S. Coll., superior colliculus; ST. Cx., ipsilateral striate cortex; ST. Cx., contralateral striate cortex.